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Prevalence And Pattern Of Seizures in Arterial Stroke Patients

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CERTIFICATE

This is to certify that this dissertation titled **"Prevalence and pattern of seizures in arterial stroke patients"** is a bonafide record of work done by **Dr. A. Sethuram,** Postgraduate student in DM Neurology, Madurai Medical College, Madurai.

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INTRODUCTION

Strokes are one of the major cause of admission in any general hospital. In the last two decades the mortality of strokes has considerably reduced because of the recognition and treatment of the various risk factors. However, even today, a large ischemic infarct carries a mortality of about 15 percent and this increases to 30-50 percent for large intra-cerebral hemorrhages, the final common terminal events being due to rise of intra-cranial pressure. The other common causes of death following strokes are aspiration pneumonia, pulmonary embolism, cardiac arrhythmias, seizures and myocardial infarction. Seizures and its complications may directly and indirectly influenze the outcome following a stroke.

Recent advances in basic and clinical research have shown potential for improvement in stroke patients, the main thrust in the field of reperfusion and neuronal protection. All these newer therapies have to be administered within a time frame which constitutes the "Therapeutic Window". Intensive stroke care units had made an impact in reducing the mortality and morbidity[1].

Seizures and Stroke are two important clinical problems in Neurology practice. Some of the patients develop seizures during acute phase of stroke, while others develop late onset post-stroke seizures. Seizures in either phase further compromises neuronal function and recovery. So seizures during and after stroke must be managed effectively.

Seizures can be a life-threatening complication of acute stroke. Status epilepticus (SE) was observed in 20% of stroke patients[2]. Other pattern of seizures like GTCS, (generalized tonic clonic seizures), partial seizures, complex partial seizures and non convulsive status epilepticus were observed in stroke patients.

Though studies considering various aspects of stroke were carried out in India, less report were available on seizures among stroke population. The present study was undertaken to know more about prevalence and pattern of seizures in arterial stroke patient and their clinical aspects, as well as to compare with the published reports. More over no such work was carried out earlier on this aspect in this hospital and this area.

REVIEW OF LITERATURE

Introduction

Post-stroke seizures can occur soon after the onset of stroke or can be delayed. Many clinical studies made a distinction between early and late seizures based on their pathophysiological differences.

Great Hughling Jackson recognized seizures as a complication that frequently occurred during the recovery phase of stroke.

Early seizures result from acute local brain metabolic alteration induced by cerebro-vascular event[4]. They result in cellular and bio-chemical dysfunction leading to electrical instability of the neurons. In contrast to early onset seizures, late-onset seizures are thought to be caused by gliosis and the development of a meningo-cerebral cicatrix.

Releasing the importance of stroke and to create public awareness World Health Organization (WHO) adopts every year July 24 as 'World Stroke Day', WHO had proclaimed 'Time is Brain'.

HISTORICAL REVIEWS

Historical references for stroke, as a cause of seizures dates back to Hippocrates in 400 B.C. Hippocrates described seizures occurring in patients at the onset of stroke. However, it was not until 1864 that Hughling Jackson clearly demonstrated stroke as a cause of epilepsy[3]. Since these times it has become clear that stroke is an important cause of seizures and epilepsy, particularly in the older age group.

Miller Fisher remarked medical person learn Neurology 'Stroke by Stroke'. Moreover focal ischemic lesion has divulged some of the most important ideas about the function of Human Brain.

Milestones on stroke and seizures is provided in the table.1 below

Table 1. The major developments in the field of stroke and seizures

19th century

Scheller (Father of Neuro-radiology) - Used X-rays for detecting Pineal calcification & observed sellar region

Egas Monitz - Person to perform and popularise carotid angiogram

Danoy - Performed Pneumo encephalography

20th century

1. Investigation

Gudfy Hounce field - Invented CT Scan

MRI - For better resolution of images since 1982

SPECT AND PET - Used for functional studies

2) Treatment

Hyper Baric Oxygen

Therapeutic Hypothermia

3) Trials

Land mark study on stroke and seizures - The Seizures After Stroke Study (SAS). Largest prospective multi centeric study.

Trials in administration of thrombolytics and neuro protective Agents

21st Century

Recent trials (on going), - Role of reterograde venous neuro - perfusion in acute stroke

Tractography - Specially modified MRI for identifying tracts

Definition

Seizures in stroke for all practical purposes is defined as, seizures occurring at the time of stroke and due to effect of stroke. It can occur either during the acute phase or during the post stroke period. Stroke defined as acute onset of focal neurological deficit of vascular etiology[34].

Seizures in stroke can be classified as follow

1) In relation to duration of occurrence of seizures following stroke
2) Pattern of seizures

Early Seizures: Seizures within 2 weeks of stroke onset.

Sub-Types of Early seizures:

- Immediate (Onset within 48 hours of stroke)
- Delayed (from 48 hours to 2 weeks)

Late onset Seizures:

After 2 weeks of onset of stroke

Very late:

-After 2 Months of onset of stroke

Epidemiology

In U.S every year 5 lakh cases of stroke are registered. Out look of these cases show 1,75,000 fatalities. Since the active early detection and management of hypertension, there has been a greater reduction in the frequency of stroke.

Studies of the epidemiology of post-stroke seizures and epilepsy are having somewhat varied results. Reports on the frequency of seizures at the onset of stroke and following stroke vary quite widely because of differing stroke patient populations, sample size, following up periods, definitions used for stroke and seizures and type of statistical analysis. In majority of studies the follow up period was less than a few months. So the documentation of late onset or recurring seizures is limited.

Hauser and Kurland etal conducted the largest epidemiological study and identified stroke as an etiology for seizures in his cases. In the Oxford Shire Community Stroke Project, the cumulative actuarial risk of having a seizure after stroke was 4.2% (95% CI, 3.7 to 15.7)[4].

Among 1,000 patients in a data bank collected in Girona, Spain, 5% of patients had epileptic seizures during the first 48 hours after stroke.

In the Seizures After Stroke Study (SAS), a prospective, multi centeric study among University Hospitals in Canada, Australia, Israel and Italy found out that 9% of stroke patients had seizures.

One of the Indian studies on seizures in stroke carried out at Chennai revealed the prevalence of seizures in stroke patient ranged from 12 to 15%

Gupta and colleagues analysed the timing of post infarction seizures. In their series 10-12% of patients developed seizures after ischemic stroke. Ninety percent of seizures occurred within the first 24 hours. Nearly 85% of seizures occurred within the first year. Only 2% developed seizures two years after stroke.[7]

The frequency of post-stroke seizures in the largest study ranged from 2% to 33%[8]. Of these 50% to 78% occurs within the first 24 hours after stroke. The frequency of post stroke seizures varies from 3% to 67%.

The overall rate of post-stroke epilepsy is approximately 2% to 4%. Early post-stroke seizures can be an independent risk factor for the subsequent development of late and recurrent seizures. One population based study found that patients with early post-stroke seizures were nearly 8 times (95% CI, 2.8 to 21.7) more likely to develop late post-stroke seizures and approximately 16 times (95% CI, 5.5 to 49.2) more likely to develop epilepsy as compared with patients without early seizures.

Seizure sub-types

Data regarding seizure subtype (simple partial, complex partial, partial with secondary generalization, or generalized) in studies of post stroke seizures are limited by the retrospective design of the majority of the studies and are potientially confounded by interviewer and recall bias related to obtaining seizure descriptions from patients or observers. Up to 60% or more seizures may not be recognized by patients[8]. Therefore, it is not surprising that different studies find different frequencies of seizure subtypes after stroke.

Approximately, 50 to 90% of early onset seizures appear to be simple partial seizures[9]. In contrast, one study reported a higher frequency (50%) of generalized tonic-clonic seizures without focal onset in patients with early onset seizures[9]. Complex partial seizures are likely under represented in these studies, as only 15% of those with complex partial seizures are aware of their spells[8].

Generalized status epilepticus can be a life threatening complication of acute ischemic stroke. Stroke may account for 25% of cases of status epilepticus in some series. A study found that 17 of 1174 patients with ischemic or hemorrhagic strokes (0.14%) developed status epilepticus, but the study did not provide data to permit calculation of subtype specific rates[2,12]. A second single institution study reported that 22 of 2742 patients with ischemic stroke (0.8%) had status epilepticus (0.1%) within the first 14 days. This compares with a 0.9% rate from a population based study. Therefore, it appears that <1% of patients with ischemic stroke develop status epilepticus (SE). On recovering from SE, some patients enter into a state of 'Non convulsive SE' - diagnosed by EEG findings of seizure activity. This entity has to diagnosed and treated effectively[2,12].

Risk factors for post stroke seizures: Hemorrhage Emboli and Ischemia (HEI)

The most consistent risk factor for seizures at the onset or following cerebral infarction or hemorrhage is cortical involvement, both in pathological and clinical studies. In the Seizures After Stroke Study (SAS) study, cerebral infarcts producing seizures were typically in the fronto-parietal lobe in the region of motor strip and extending down to the insula. The anterior hemispheres and carotid arterial territory are sites of brain infarction with a higher risk of seizures.

With respect to intra cerebral hemorrhage, lobar hemorrhage carry a higher risk of seizures compared to those located sub-cortically. Deep cerebral and brain stem infarcts and infra-tentorial hemorrhages have not been commonly associated with seizures.

Patients with brain hemorrhages have seizures more often than those with infarcts. In the Lausanne stroke registry, 7% of intra cerebral hemorrhage patients had seizures during acute stroke compared with less than 1% of patients with ischemic stroke.[5] In the Harvard

stroke registry, 6% of patients with hematomas had seizures during acute phase.[6] Sub-cortical 'slit' hemorrhages are most often accompanied by seizures. Among patients with brain infarcts those patients who have large and hemorrhagic infarcts have the most likelihood of developing seizures. Patients with lesions that include the cerebral cortex have a much higher frequency of seizures than those whose lesions are only sub-cortical.

Patients with embolic brain infarcts of cardiac origin have a much higher frequency of seizures than those who have large artery occlusive disease.

Cerebral embolism is one of the important causes of stroke particularly in young patients. The incidence of cardiac embolism varies in several studies. It is as low as 3% in community studies and as high as 30% in referral centres; but 15% of patients with stroke.

Seizures and Stroke sub types

The greatest risk of seizures following intra cerebral hemorrhage compared to infarction has been noted. Seizure risk does not appear to increase with the amount of ventricular or cisternal blood, nor the presence of hydrocephalus or shift of intra-cranial structures.

Sub-cortical infarctions are less commonly associated with seizures than cortical. Seizures have been noted in up to 3% of patients following lacunar stroke. However, some have proposed that lacunar strokes are a marker of more wide spread vascular disease rather than being directly responsible for stroke related seizures.

Seizures have been noted up to 23% of patients with striato-capsular infarction. It is possible that CT under estimates the number of patients with cortical ischemia in this form of sub cortical stroke. A more sensitive indicator may be single photon emission tomography (SPECT), positron emission tomography (PET) or magnetic resonance imaging (MRI). The mechanism is cortical tissue can be functionally dearanged in sub-cortical infarction and therefore involved in seizure production.

Less than 2% of patients with Transient Ischemic Attack (TIA) experience seizures.

However, distinguishing a TIA from a focal seizure can sometimes be difficult. This is particularly true in cases of limb-shaking variant TIA'S[32,33].

Seizures in regard to stroke location

Cortical location is the best characterized risk factor for early seizures following stroke. Although seizures seem to be more common after strokes with cortical involvement, they may also occur in the setting of sub-cortical stroke, as already mentioned, due to a possible consequence of a substantial release of glutamate from axon terminals arising from injured thalamo cortical neurons.

Among 770 patients with supra tentorial brain infarcts, the presence of cardiac origin for brain embolism, had a relative risk of 5.14% developing early seizures compared with patients without cardiac-origin embolism. Post stroke seizures can occasionally cause worsening of neurologic deficits.

Seizure and stroke size

Larger strokes, especially cerebral infarctions, have been associated with an increased risk of seizures. However, patients with small lobar hemorrhages, because of their cortical location, experience seizures more often than patients with large bleeds located elsewhere by Berger et al (1988) and Bladin et. al. (1996).

Stroke mechanism

Some studies have reported a presumed embolic cause of stroke more often than thrombotic among patients with seizures after stroke, (Richardson & Dodge, 1954; Mohr et al, 1978) others have not found this association, (Black etd.1983; Kilpatrick et al.1990). One must consider the limitations of diagnosing a cause of stroke in individual patients because of variety of clinical presentation, investigatory limitations and co-existence of several risk factors (Ramirez – Lassepas et al, 1987; ladder et. al. 1994, Madden et. al. 1995).

Post stroke late seizures

Although post stroke late seizures occur after first two weeks of stroke, these may begin

months to a year after stroke. The incidence of post stroke late seizures is about 15%. The interval between stroke and onset of seizures vary widely. Nearly 24% of seizures occur within first week and 93% in 2 years. The prevalence of late seizures is high in patients with permanent neurological deficits or those needing rehabilitation. Primary generalized seizure is common with late onset seizures (56%) compared to early onset seizures, which are generally simple partial in nature. Status epileptics is more frequent in early-onset than late onset seizures.

Post stroke risk of epilepsy

The incidence of recurrent seizures (epilepsy) after stroke in a large prospective multi-center study is 2.5%. The possibility of recurrence is greater in late onset (58%) compared with early onset seizures (12%). In a population based study from Rochester, Minnesota the cumulative probability of developing initial late seizures was 3.0% by 1 year, 4.7% by 2 years, 7.4% by 5 years and 8.9% by 10 years. The risk of recurrence during the first year was 23 times higher for initial late seizures and 17 times higher for epilepsy when compared to population in a community[23]. In a retrospective follow up study of 200 consecutive stroke patients, 15% developed seizures within first two weeks after stroke. Late onset of the first seizure is an independent risk factor for epilepsy after ischemic stroke but not after hemorrhagic stroke[24,25]. However some studies have recorded high prevalence of late seizures in putaminal and lobar hemorrhages. Supratentorial brain infarcts especially cortical is associated with seizure recurrences despite anti-epileptic drug treatment. Sub cortical infarcts are associated with infrequent early seizures and a very low one-year risk of recurrence. Patients with a large brain infarct involving the supra-marginal or superior temporal gyrus have 5 times increased risk of late onset seizures, while patients with a cardio-embolic infarct

involving the middle temporal or post-central gyrus, had 8 times increased risk of early onset seizures. Patients presenting with severe strokes due to total anterior circulation infarction are also at a high risk for recurrent seizures[26]. The incidence of late seizures is higher in patients with left cortical infarction (29.3%) than those with right one (15.4%) suggesting that left sided cortical involvement may have some liability to late onset seizures[27]. Recurrent stroke increases the risk of initial late seizure or epilepsy[28].

Seizures Preceding stroke

Barolin (1982) coined the term vascular precursor epilepsy for seizures preceding stroke. Most of his patients with focal seizures experienced definite stroke of the relevant hemisphere within a year. He felt that such focal seizures were just as important as a sign of impending stroke as transient ischemic attacks and an opportunity for prophylactic therapy. Cocito et. al (1982) reported that seizures (focal) may be the sole manifestation of sub total or total internal carotid occlusion and recommended a cerebra vascular assessment and risk factor management for patients with other wise unexplained seizures.

Further evidence for the epileptogenic potential for silent cerebral infarcts came from a study by Shinton et al (1987) who showed an increased frequency of preceding epilepsy in first stroke patients compared to age sex and race matched controls. In addition, patients with late onset unexplained epilepsy may have a higher prevalence of silent ischemic lesions on CT brain compared to age and sex matched controls.

The mechanism of silent ischemia and associated seizures may relate to internal carotid artery stenosis or occlusion and associated embolism, or hypo-perfusion.

Post stroke late status epilepticus (SE)

The incidence of SE in post stroke first time seizure patients is 9% at the end of 3.7 years. There is no relationship between the occurrence of SE and stroke risk factors, stroke type, stroke topography, cause, and cortical involvement, size of lesion, and seizure type or EEG findings. SE occurred more frequently among patients with higher disability rating. Early onset SE is associated with a higher risk for SE recurrence. Management is similar to any other SE[35].

Seizures following Interventions

Seizures are infrequent following carotid end arterectomy (CEA). Seizures may be secondary to cerebral embolisation from the operative site or due to disturbance of cerebra vascular auto-regulation following CEA leading to a hyper-perfusion syndrome or both. Seizures occur one to two weeks after CEA[13] may be focal on generalized. Response to phenytoin is good.

Etio pathology

The etio pathology can be divided as

a) Bio chemical theory
b) Electrical theory
c) Mechanical theory.

Bio chemical theory

Acute cerebro-vascular event leads to increased extra-cellular concentrations of an excitotoxic neuro-transmitter glutamate. Glutamate has been associated with secondary neuronal injury.

Electrical theory

Recurrent epileptiform-type neuronal discharges can occur in neural networks of existing neurons exposed to this neuro-transmitter. Experimental proof suggest that epileptogenesis is enhanced also by hyperglycemia at the time of ictus.

Peri-infarct area depolarizations have been observed in the penumbra after a stroke. There is a correlation between the number and the total duration of depolarizing events and infract volume in the setting of ischemia perhaps due to reductions in capillary perfusions leading to more profound ischemia in the penumbral tissue.

Mechanical theory

Due to the effect of raised intracranial hypertension

Supportive evidences

a) Experimental

b) Neuro Anatomical

c) Physio - chemical changes

For the development of seizures in stroke the causes for inter relationship between different mechanisms are discussed below.

Experimental

Experimental studies in laboratory animals suggest that repeated seizure like activity in the setting of cerebral ischemia significantly increases infarct size and can impair functional recovery. Other laboratory animal studies indicate that some antiepileptic drugs may impair recovery after stroke or other forms of focal brain injury. Phenytoin, when given alone or in combination with an intracortical infusion of γ-aminobutyric acid (GABA), delays recovery of motor function after focal brain injury[29]. Phenobarbital and benzodiazepines may also retard the recovery process[29,30]. In contrast, there has been no demonstrable effect of carbamazepine on postbrain injury recovery.

Whether or not similar detrimental effects seen with certain anticonvulsants in laboratory animals. Also occurence of seizures in humans recovering from stroke is not yet finalised .

Neuro Anatomy

Anteriorly the brain is supplied by two internal carotid arteries and their branches (i.e middle cerebral artery, anterior cerebral artery, anterior chorodial artery and their branches). Posteriorly by the two vertebral arteries which unites to form a common trunk, the basilar artery and its branches. (i.e posterior cerebral artery and end arteries). Collateral arteries play an important role in cerebral circulation. The main ones are as follows.

1. The anastomosis around the orbit formed by the branches of the external carotid artery with ophthalmic artery.

2. Circle of Willis formed by anterior communicating arteries which connect the two anterior cerebral arteries, and post communicating arteries which connect the internal carotid arteries to the post cerebral arteries.
3. Cortico-pial network

Lack of blood supply (or) steal of circulation leads to hypoxic brain injury in a local area. As a result physio-chemical mechanism are initiated which may contribute to seizures.

Physio- chemical changes

More than any other organ, the brain depends from minute to minute adequate supply of oxygenated blood. The 1400gm of brain would require 150gm of glucose and 72 liters of oxygen per 24hrs. Constancy of cerebral circulation is maintained by a series of baroreceptors and vasomotor reflexes and by auto regulation.

Investigations

After detailed history and meticulous neuromedical examination which includes palpation and auscultation of heart and major vessels, the importance and priority of any investigation in acute stroke should be the clinical judgement. The importance of fundus examination and its vasculature for disease and embolic fragments needs greater emphasis. Taking CT scans in the absence of clinical examination & provisional diagnosis should be avoided.

Chest X-ray, serial ECG, Echo-cardiogram are essential to assess cardiopulmonary status, cardiac monitoring only when required.

Complete hemogram, bleeding time, and pro-thrombin time are screening test for assessing hematological profile. Routine screening of blood sugar, urea, lipids, uric acids and electrolytes are base line investigations. Special test for detection of sickle cells, LE cells, VDRL, HIV, RA factor, electroporetic pattern are performed if needed.

Electro-encephalography (EEG), is not of specific value, but shows slowing of waves on the side of infarct, PLEDS (Periodic Lateralized Epileptiform Activity) can be seen and phase reversal can be observed. Epileptiform activity can be seen if there is evidence of seizure activity.

The role of EEG in the differential diagnosis of vascular hemiplegia is very little. The main practical utility is its ability, to distinguish an acute lesion in the distribution of the internal carotid artery (or) other major cerebral artery, which produces, an area of slowing in the appropriate region. In contrast, deep lacunar lesions in the brainstem (or) cerebrum, the surface EEG is usually normal, despite prominent clinical manifestations. After 4 to 7 months,

roughly 50 to 60% of patients with infarction in the territory of middle cerebral artery have a normal EEG. A persistent abnormality is associated with a poor prognosis for further recovery. Large lesions of midbrain produce bilaterally synchronous slow waves, but those of the pons and medulla are not associated with EEG changes.

In addition to slow wave foci, other less dramatic changes occur in the EEG, ipsilateral diminution of frequency (or) amplitude of the alpha rhythm (or) both together – is common, particularly in occipital infarct. Diffuse random theta activity may also be present.

Gastaut and Glove (1960) found that in many elderly patients with chronic vascular insufficiency of sylvian region, rhythmical paroxysmal delta activity was present in one or both temporal region. This slow activity was increased by ipsilateral carotid compression or inhaling nitrogen. The risk of cerebral infarction is high in these patients and the recognition of these EEG abnormalities has prognostic value.

Epileptiform discharges are very unusual in the acute phase of a vascular lesion but become more and more common with the passage of time; sharp wave (or) spike foci are well recognized sequelae of cerebral infarction[31]. Chartian, Leffman, and Shaw (1964) described a number of patients with epileptiform discharges which appeared within hours or days of the infarct.

Computerized cranial tomography (CT scan); is a single most important non-invasive investigation to distinguish infarction from hemorrhage. It’s limitation is non detection of infarction within 48 hours of early infarct.

Carotid and trans-cranial Doppler study helps to understand hemodynamic status, but it is not accurate enough to replace conventional four vessel cerebral angiogram.

Role of Magnetic Resonance Imaging (MRI) and positron emission tomography (PET) are also helpful in detecting early ischemic changes. Proton density MRI helps to identify the extent of infarcted tissue within hours of onset.

Regional cerebral blood flow mapping by non-invasive (Xe-133) isotopic inhalation technique and PET with the use of labeled CO_2 and O_2 provide, qualitative and quantitative tomographic assessment of CBF (Cerebral Blood Flow). However PET is still a research tool.

Digital substraction angiography (DSA), by intravenous route, not only outlines the entire brachiocephalic circulation but is relatively safe and less invasive procedure.

SPECT (Single Proton Emission Computed Tomography) imaging technique relies on the Gamma-emiting properties of radioligands such as 99m TC hexa-methylprophlenamine oxime (HMPAO). SPECT scanning helps to localize the vascular territory affected and to assess the prognosis.

For early recognition of both stroke and seizures, one needs basic clinical examination as the foundation step. Any amount of investigation only supports the clinical examination but never substitutes it. Hence, one should recall the sayings, of Sir William Osler-“Good history and detailed clinical examination is the best investigation for better patient care”.

Management

The drug treatment of post-stroke seizures is similar to that for patients with epilepsy

resulting from other causes. In patients with partial or generalized seizures following stroke, carbamazepine and phenytoin have the highest treatment success. Phenobarbitione, primidone and valproic acid are second line of choice. Seizures can be controlled well with monotherapy[7] Although early seizures occurrence increases risk of subsequent seizures, chronic anti-epileptic drug treatment may be warranted only in the presence of cortical involvement caused by infarct or lobar hemorrhage.

Anti Epileptic Drugs (AED)

The first decision confronting the physician is whether to use the conventional AED or one of the newer AED in the elderly patient with post stroke epilepsy. The present knowledge regarding the role of newer AEDs in post stroke epilepsy is limited. Gabapentin may be a good choice due to its safety profile and absence of drug interactions. But its major disadvantages are thrice daily dosing regimen and reduced clearance in renal disease. The advantages of lamotrigine include good overall safety profile, no significant drug interactions and twice daily dosing. It should be considered for patients with severe renal disease because it undergoes hepatic metabolism. The major limiting factor with lamotrigine is the risk of rash. Both topiramate and tiagabine have least side effect profiles and are associated with few drug interactions.

Duration of treatment

Chronic anticonvulsant therapy is recommended for post stroke late seizures. Patients and their family members should be convinced of the need for long (may be life long) duration of therapy. Most strokes related seizures are partial and partial seizures generally have a poorer prognosis. Presence of neuropsychiatric handicap is another limiting factor, for administering long-term anticonvulsant treatment. Presence of cortical lesions, short periods between seizures, the severity of the seizures and associated toxic metabolic disorders have an adverse effect on the long-term prognosis. Arteriovenous malformations, vasculitis and possible embolic causes of stroke also tend to result in more persistent seizures. The role of EEG in

making the decision to discontinue AED is limited.

Prognosis and Rehabilitation

Stroke severity is the most important determinant of outcome in stroke patients. Although mortality rates in stroke patients with status epilepticus (SE) can be high, data reflecting the independent effect of postischemic status epilepticus on outcome is limited because it is confounded by other factors relate to the stroke, particular stroke severity. Another prospective study reported an almost three fold increase in mortality among patients with acute ischemic stroke and generalized convulsive SE as compared with patients with active ischemic stroke alone (39% versus 14%, $P<0.001$).[19]

Late onset seizures have a minimal impact on rehabilitation and functional outcome[20,21].

Future Prospects

Epidemiological studies can be undertaken to identify the inter and intra regional variability in the occurrence of seizures in stroke population. Predictive markers can be identified to detect the occurrence of seizures in early phase of stroke.

Conclusion

Seizures can occur in stroke patients. Till date there is no tell-tale evidence to predict which patients will develop seizures. Hence a study of seizures in stroke is a great value for epidemiological, clinical and research work.

Aim of the Study

1. To find out the prevalence of seizures in arterial stroke,
2. To analyse the pattern of seizures among them,
3. To identify the time of occurrence of seizures,
4. To correlate the pathological status in relation to stroke patient who had seizures,
5. To elicit the response to anti-epileptic drugs in those cases and
6. To determine the nature of clinical course in those individuals who develop recurrent seizures.

Materials & Methods

Settings

The present work was carried at the Department of Neurology of a tertiary care medical college hospital.

Collaborating Department

The work was carried out with the help of Departments of Medicine, Cardiology, Radiology and Bio-Chemistry.

Ethical Approval

Institutional ethical clearance was obtained before proceeding with actual work.

Consent

An informed consent was obtained in those patients included for the study.

Design of study

A cross sectional study was conducted among stroke patient admitted to this hospital.

Period of study

Study period ranged from July 2004 to June 2005.

Sample size

A total of 540 cases of stroke were registered during the study period formed the basis for the study.

Inclusion criteria

1. Patients above the age of 15 years presenting with acute stroke for the first time.
2. Patients not fitting in with the exclusion criteria.

Exclusion criteria

1. Children less than 15 years of Age.
2. Stroke like presentation due to surgical causes like trauma, brain abscess, arterio-venous malformation and tumour.
3. CNS infections producing arteritis.
4. Inflammatory and Demyelinating disorders.
5. Known seizure patient and psychiatric patient.
6. Second time strokes.
7. Stroked due to post thrombolytic state
8. Post cardiac arrest resuscitation state
9. Patients on anticoagulants and antiplatelet agents.
10. Metabolic disorders like chronic diabetics and other endocrine disturbances.
11. Patients with cancer
12. Post-iradiational stroke.
13. Pregnant women
14. Stroke due to substance abuse like alcohol, drug addiction and cocaine.
15. Nonwilling and non co-operative patients.

Definitions used for the study

Stroke

Acute onset of focal neurological deficit of vascular etiology. It can be either due to hemorrhage, emboli or thrombosis (H.E.I)

Age Group Classification

According to W.H.O. (World Health Organisation), the patients are grouped as follow

Adolescent age group between (15 to 24) years

Young age between (25 to 44) years

Middle age between (45 to 64) years

Elder age between (65 to 74) years

Very Elderly between (75 to 84) years of age

Old age (85 and above)

Data collection

Socio, demographic data, clinical and investigatory data were collected.

Patient admitted with clinical diagnosis of cerebero vascular accident above 15 years of age were included in the study. A detailed clinical history was elicited and meticulous neurological examination was carried out followed by routine investigations like total count, differential count, Hb, ESR, chest X-ray, electrocardiogram, echocardiogram (selected cases), trans-oesophageal echocardiogram (Selected cases only) were carried out. Special neurological tests like CT scan brain, MRI was planned for suspected posterior circulation strokes only due to economic constraints. EEG was also carried out in stroke patients.

If the patient develops seizures, a clinical history of nature, type and pattern of seizures were analysed. A specific question of secondary generalization if present (or) not was also elicited. Enquiry about the worsening of existing neurological deficit was also asked. Presence of complex partial attacks (CPS) and status epilepticus (SE) were specifically enquired and looked for.

Inter-ictal electro-encephalography studies were carried out in these patients. If seizures occurs anti-epileptic drugs (Tab.phenytoin 100mg 2HS) was administered. The response to the drug was assessed and tabulated. Persistence of seizures even after anti-epileptic drugs were looked for. The nature and type of seizures and the stroke pattern were correlated Subsequent development of post-stroke epilepsy was enquired and the patient were followed up for three months. Any further worsening of the neurological status was noticed and recorded.

Follow up

These patients were followed up continuously in the hospital until discharge or death during their stay. Later they were followed up to three months either in person or with the help of relatives who were trained to look for seizures and to report to the principal investigator about the occurrence of seizures. The study is limited to 3 months in view of most of previous published reports on stroke.

Bias of the study

Information Bias

In aphasic individuals, information was taken from available informant & subsequently confirmed from the close care taker of the patient.

Observer Bias

Seizures as reported by relatives were considered. However to confirm the type of seizures, relatives were shown video clippings of various seizure patterns and asked to identify the type of seizures, based on which the pattern of seizures were analysed.

A patient developing seizure in the hospital was seen immediately after a call from the ward and confirmed clinically, by interrogating with the concerned resident in charge of the case.

Investigation methods

Bio-chemical investigations were standerised and carried out in the Department of Biochemistry. Echocardiogram was done in Department of Cardiology by qualified Cardiologist.

CT scan brain was done within (24-48 hours) of admission, by Hitachi Scan machine (1997). Serial 10mm axial cuts were done. Contrast scan was done in selected cases only.

MRI was done in selected cases of suspected post circulation stroke. It was done with the help of 1.5 Tesla unit machine.

EEG was done within (48-72 hours) on admission in all cases.

End point of the study

The end point of this study were

i) Follow up of the cases during their hospital stay.

ii) 3 months after their discharge

iii) Death of the patient.

Financial support

This study was not supported by any funding agency.

Limitations

i) Only patients with acute and arterial strokes were analysed.

ii) Possibility of observer and informant bias.

Competing interest

No conflict of interest was seen for the study purpose.

Statistical analysis

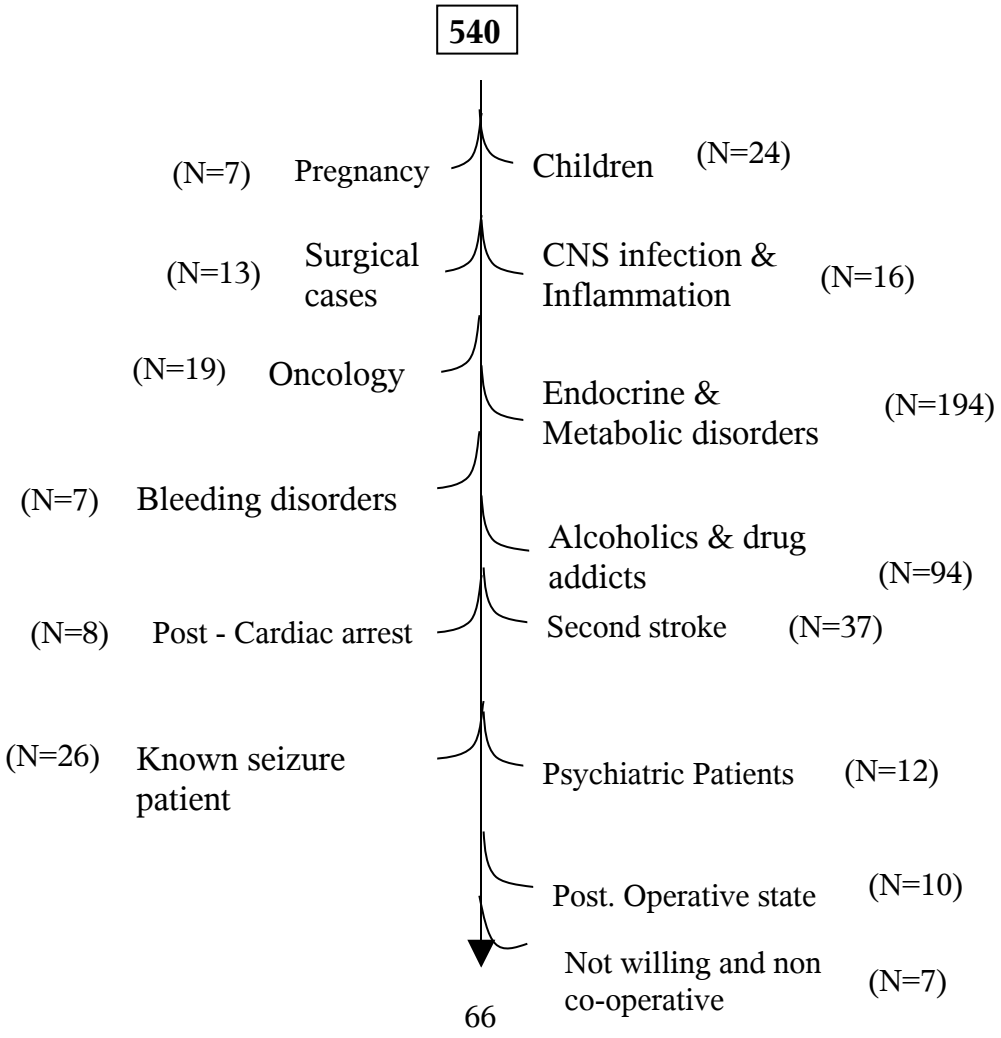
Simple descriptive statistical analysis was applied.

Results

During the study period 540 cases were enrolled. The patients flow diagram for the final inclusion is shown below.

Flow diagram for case selection

Total No: 540



(N=Number of cases)

Social & Demographic aspect

All the 66 patients belonged to low socio-economic status. There were 45 males and 21females. Their age ranged from 19 to 79 years of age. Mean age was 50.4 years. 20 individuals were below the age of 45 years, the rest were 45 years and above.

The occurrence of seizures in relation to age & gender is depicted in Table No. 2 given below.

Table: 2

Seizures in relation to age and gender

Characters		Seizures	Percentage
Total No. of cases	66	10	15
Gender			
Male	45	7	15.5
Female	21	3	14.2
Age group in years			
below 45 years	20	3	15
above 45 years	46	7	15.2

Clinical observation

Features suggestive of anterior & posterior circulation stroke were seen in 56 and 10 cases respectively. The distribution of stroke & seizures in relation with territory is given in table No.3

Table No: 3

Distribution of Seizures in Relation to stroke territory.

stroke territory	No. of Cases	Seizures	Percentage
Anterior circulation	56	9	16.1
Posterior Circulation	10	1	10
Total	**66**	**10**	

The other clinical observations noticed include hypertension in 24 cases as per Joint National Committee (JNC) VII criteria, rheumatic heart disease were observed in three cases.

Seizures timing

Out of the ten cases of seizures, seven cases developed seizures within 48 hours of stroke, depicting the fact that acute neurological insult reduces the seizures threshold. Table No.4 gives details about timing of seizures.

Table No: 4

Distribution of cases according to timing of seizures

Early seizures, (within 2 weeks of stroke onset)	Number
Immediate (onset within 48 hours)	7
Delayed (48 hours to 2 weeks)	3
Late onset seizures	
Above 2 weeks	0
Very late (2 months and above)	0
Recurrent seizures (post stroke seizures)	2

Radiological finding

The diagnosis were confirmed with the help of CT and MRI, and their location of brain infarct given in TableNo.5

CT and MRI Findings in relation to infarct

Location of infarct	Number
Cortical infarct	16
Corona radiata	6
Capsulo ganglionic infarct	20
Lacunar infarct	3
Thalamic infarct	1
Brain stem infarct	1
Multi infarct	2
Total	**49**

A total of 5 cases showed hemorrhagic lesions and their location as revealed by CT is provided in table number 6.

Table No: 6

CT Findings in relation to hemorrhage

Location of hemorrhage	Number
Putaminal bleed	3
Thalamic bleed	1
Intra cerebral bleed (lobar) tempero parietal	1

MRI was done in two cases which revealed brain stem infarct.

Case distribution according to imaging findings and pattern of seizures are provided in table No.7

Table No: 7

CT findings and pattern of seizure

Imaging findings brain CT scan	No	Pattern of seizure	No
Infarct total number	49	Partial seizure	7
-		Generalized seizure	2
Haemorrhagic lesion	5	Partial seizure	1
-		Generalized seizure	0
Normal CT scan finding	12	-	-
Total	**66**		**10**

EEG patterns

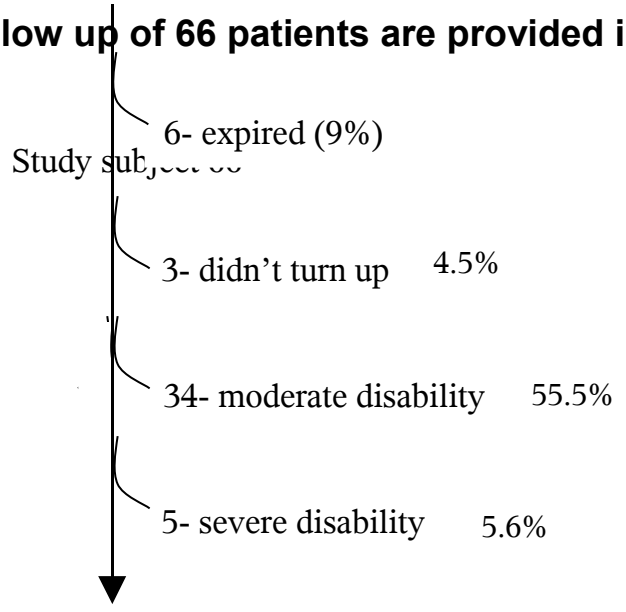
EEG analysis revealed spike and sharp waves in 10, Slowing of waves in 7, PLEDS in 1, and Phase reversal in 1.

Table No: 8

Details of stroke, CT and MRI findings, types of seizures and EEG findings

Follow up

Details of the follow up of 66 patients are provided in the flow diagram given below



Discussion

Seizures were noticed in stroke patients and the reason for seizures were multiple. In view of age and confounding factors, as well as availability of multiple drugs for controlling seizures, the subject of seizures in stroke patient did not gain much importance. This was reflected very much from the published literature on seizures in stroke.

Analysing 66 patients with arterial stroke, 10 patients had seizures, seven of the 10 patients had seizures within 48 hours of onset of stroke and three of the 10 patients developed delayed seizures (48 hours to two weeks).

Recurrent seizures were seen in only two patients. Of these, one turned to be multi-infarct state and other had occipital infarct, seizures were due to poor drug compliance in the occipital infarct patient. Late onset (above 2 weeks) and very late (above 2 months) were not observed.

All of them received anti-epileptic drug (T. Phenytoin 100mg two at bed time).

Epidemiological Aspect

Post stroke seizure is a common problem faced by every physician in practice. Its impact on patient's morbidity and mortality stimulates many research workers especially clinical and epidemiological. Unfortunately complete epidemiological study is lacking in this area both India and abroad. In patients over the age of 50 years, the cause of seizures is vascular in approximately 30-40%.[15.]

Stroke is the leading cause of seizures in the older population, especially beyond 60

years of age. Cerebral vascular disease (infarction (or) hemorrhage) accounts for 14 to 54% of diagnosed cases of seizures in older patients according to the most recent studies (1998). A similar trend in the age specific incidence of seizures was seen in the community base study carried at Rochester, Minnesota, USA by Hauser etal (1992). The present observation on seizures corresponds well with the reports from USA.

Stroke location & seizures

Cortical location is the best characterized risk factor for early seizures after stroke and this observation is also widely supported by studies conducted already. Out of the 10 patients with seizure, four patients had infarct in the cortical region (40%). This finding corresponds with the Seizures After Stroke Study (SAS) which quotes that cerebral infarcts producing seizures were typically in the cortical region of the motor strip and extending down to the insular region.

The comparative study of distribution of seizures in relation to location is given in table no.9

Table No.9

Comparative Analysis of Location of Stroke Among patients with stroke

No.	Stroke location	Present study (2004-05)	Berger et.el 1988	Weisberg et.el (1991)
1.	Anterior (carotid)	16.1%	12-15%	18%
2.	Posterior (vertebro-basilar territory)	10%	6-8%	3.7%

Pathological Correlation

Haemorrhage and infarction (H&E)

Studies of early and late onset post stroke seizures where patients with pre-stroke seizures, were largely excluded and CT was used in the diagnosis of cerebral ischemia (or) hemorrhage in all these patients were summarized in relation to the present report in table number 10.

Table No.10

Frequency of early and late seizures following cerebral infarction or hemorrhage in CT scan confirmed cases.

Characters	Kilpatrick et al.,	Davlos et al.,	Lanceman et al.,	Giroud et al.,	Lo et al.,	Arboix et al.,	Reith et al.,	Bladin et al.,	Present Study
Year	1990(1)[a,b]	1992(2)[a,b]	1993(1)	1994(2)[a]	1994(1)[a]	1997(2)[a]	1997(3)	1998(4)	2004 (1)
Total patients	1000	1000	219	1640	1200	1220	1195	1897	66
Number of infarcts	601	662	183	1213	696	1012	900	-	49
hemorrhage	65	156	36	129	384	208	75	-	5
Follow-up	7 months (mean, early seizures only)	Not stated	11.5 months (mean)	None	None	Not stated	Not stated	9	3 months
Infarction %	6.5	5.4	3.8	7	2.3	2	3	-	18%
Hemorrhage %	15.4	8.3	14	16	2.8	4.3	8	8	20%

1 = Hospital stroke patients, 2 = Stroke registry/database, 3 = Hospital/community database, 4 = Multicentre hospital stroke patients.

[a] includes patients with TIA and/or subarachnoid haemorrhage and/or unclassified stroke types.

[b] includes underlying causes of haemorrhage such as arteriovenous malformation, coagulation disorders.

[a] All studies were CT supported, largely descriptive, with only two (Berger et al. and Faught et al.) having limited univariate analysis with delineation of risk factors for seizures.

[b] Study includes patients with underlying causes such as neoplasm, aneurysm, mycotic aneurysm, anticoagulant complication, endovenous malforamation and angioma.

[c] Includes patients with seizures before cerebral haemorrhage.

[d] Massive haematoma defined as >50ml/s.

The difference in the occurrence of seizures when compared with other studies, may be

attributed due to strict inclusion criteria and rigid case selection, and inclusion only of arterial stroke patient, while other studies had included all causes of stroke.

A comparative analysis of seizures in hemorrhage is provided in table number. 11

Table No.11

A comparative analysis of seizures in hemorrhage

	Berger et al., 1988[b]	Faught et al., 1989[c]	Sung & Chu, 1989[b]	Weisberg et al., 1991[b]	present study (2004-05)
Number of patients	112	123	1402	222	66
Follow-up duration (months)	2 (median)	55 (mean)	20-22 (mean)	12	3 months
Seizures (%)	17	25	5	15	20%
Late seizures (%)	-	6	2	3	Nil
Location of hemorrhage					
Lobar / cortical	26	54	32	30	1
Thalamic	-	0	2	4	1
Basal ganglia	-	17	2	3	3
Massive[d]	-	5	-	-	0

Seizures pattern

Status epilepticus (SE) is rarely reported following stroke all though none of our patients had SE (both convulsive and non-convulsive SE). Only one study by Bladin (1998) had reported 13% incidence of SE in stroke patients. Lobar hemorrhages are commonly associated with SE than other types of intracerebral hemorrhage. However, CVA is one of the causes of SE in older patients. In addition, the mortality of SE increases with advancing age (beyond 60 years) and duration of seizures. Hence the importance of early recognisation and management of seizures must be disseminated to the practioner and care provider. The other reason of SE after stroke are anti-convulsant withdrawal and non-compliance and this should be kept in mind before making decision.

Present study indicated that 8 patients of those with post-stroke seizure had partial

seizures of simple motor type. However, primary generalized seizure were observed in 2 patients (20%). Complex partial seizure convulsive and non-convulsive status epilepticus were not observed.

Partial seizures predominate after cerebral infarction and hemorrhage by a study conducted by Fraught (1989) and Lowenstin et al (1990). Similar to our study, partial seizures of simple motor type was the most common. It is possible that in many patients focal onset of seizures is un witnessed or not appreciated and can mislead.

Out of the ten cases two had generalized seizure. This correlates well with other studies.

EEG correlation

EEG was abnormal (disorganized background, spike and sharp waves PLEDS) in 19 of 66 cases (28.8%) while clinical seizures were noticed in 10 of them.

Epileptiform discharges are important for early recognition of status epilepticus risk. The development of seizures and particularly status epilepticus can affect the outcome of stroke patients due to synergistic effect of combined injuries of status epilepticus and ischemia. The presence of epileptiform discharge on EEG examination, which occurs in approximately (85-90%) of cases of post stroke seizure is an important predictor for ongoing or recurrent seizures.

Strength of the study

1. A rigid criteria was adapted for inclusion of cases.
2. These cases were followed up over a period of three months continuously.

3. The family members were trained to recognize seizures.

Limitation

1. The study was limited to acute first time stroke only.
2. The study included only arterial strokes.
3. The follow up of cases could not be implemented beyond 3 months due to technical, social and cultural constraints
4. The prevalence and pattern of seizures varied in different series which could be attributed to observer (or) informer bias as well as criteria adopted for case selection.
5. Advanced statistical methods and formula could not be applied as the number were small.

Future works

The scope for research is plenty in the field of seizures in stroke. Right from epidemiology up to molecular biology, the areas are wide open. To analyse the inter and intra regional variations, in epidemiological and clinical parameters will be useful. Impact of seizures on prognosis and rehabilitation can be further studied. Similarly development of seizures in the patient with and without EEG changes needs to be addressed.

Experimental studies can be conducted for analyzing the effect of anti-epileptic drugs and their inter actions.

Conclusion

1. The prevalence of seizures in arterial stroke was 15%
2. Pattern of seizures observed were partial seizure in 8 and generalized seizure in 2 cases.
3. Complex partial seizure (CPS) and status epilepticus (SE) were not observed during the study period.
4. The median time for the occurrence of seizures in arterial stroke was 12 hours. However, it ranged from 0-72 hours in hospital follow up.
5. Recurrent seizures were seen in two only.
6. Occurrence of seizures in arterial stroke was independent of age and gender.
7. Seizures were noticed more among those with hemorrhagic lesion (cortical) and in those who had anterior circulation stroke.
8. Seizures were well controlled with oral phenytoin in all except two during the follow up period. The reason for failures were poor drug compliance in one and extensive stroke in other case.
9. Epileptiform activity in EEG were noticed in 19 cases of arterial stroke out of which only 10 developed clinical seizures.
10. During the three month follow up six of the 66 (9%) expired and three were lost for follow up.

Summary

Seizures were observed in arterial stroke. It has an impact on the natural course and outcome of stroke cases. In view of scanty literature in this area of stroke, an attempt has been made to find out the prevalence and pattern of seizures among arterial stroke cases with special reference to time of occurrence, underlying pathological status and response to anti-epileptic drugs.

A cross sectional study was designed after institutional ethical approval to study 540 cases of stroke admitted to a tertiary care teaching hospital over a period of 12 consecutive months. A rigid inclusion and exclusion criteria were adopted to select cases of first onset acute arterial stroke. They were evaluated clinically and by investigation methods to find out the occurrence of seizures among them. Their data were analysed by simple descriptive statistics.

Out of the 540, only 66 (male -45, female-21) patients satisfied the inclusion criteria. Their age ranged from 19 to 79 years and the mean age was 50.4 years. Seizures were noticed in 10 of 66 (15%) of patients, during their stay in the hospital (range: 24 hrs to 2 week) and the medium time for the onset of seizures was 12 hours (range- 0 to 72 hours). In seven cases seizures occured within 48 hours, three of the remaning developed delayed seizures. Recurrent seizures were seen in two cases.

The occurrence of seizures were independent of age and gender. However it was more in

the anterior circulation and in those with hemorrhagic lesion (cortical). Seizures responded well with oral phenytoin sodium. Though epileptiform discharges were noticed in 19 of 66 cases (28.8%) of arterial stroke, seizures were noticed clinically in 10 of them only. During the three month follow up, six of the 66 (9%) expired and three were lost for follow up.

Present observations were inconsonance with published reports. In view of occurrence of seizures in stroke patients, the treating practioner should take utmost care to look for seizures, and two create awareness among health care professionals and family members. First line of anti-epileptic drug gave a satisfactory response. Prophylactic anti-epileptic agents may be of used in those with cortical lesions.

Proforma for study of Prevalence and Pattern of seizures in stroke patients

Name	**:**	**Income**	**:**
Age	**:**	**Habits**	**:**
Sex	**:**	**O.P. No.**	**:**
Address	**:**	**I.P. No.**	**:**

Stroke Clinical Presentation:

Anterior circulation symptoms & signs	**:**	mono paresis, hemi paresis, speech and auditory disturbances	**Yes/No**
Posterior circulation symptoms & signs	**:**	visual, vertigo, brain stem features and sensory disturbances	**Yes/No**

Investigatory Parameters

Bio-chemical

CT scan brain

MRI brain

SEIZURES AND ITS VARIOUS PATTERNS **Yes/No**

A-Early onset seizures B-Late onset seizures

GTCS

Partial seizures

Myoclonic

Other types

AED used

Response to AED **Yes/No**

Status Epileptics **Yes/No**

Convulsive

Non-convulsive

EEG CHANGES **Yes/No**

Follow up after 3 months (for seizures)

Controlled **Yes/No**

Persisting

Others

Remarks & observations if any

CRF : Chronic Renal Failure **CT:** Computerised Tomogram

DM : Diabetics Mellitus **EEG:** Electro Encephalography **GTCS:** Generalised Tonic Clonic Seizures **HT :** Hypertension
MRI: Magnetic Resonance Imaging

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From

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To

The Controller of Examinations,

The TamilNadu Dr. MGR Medical University,

Chennai.

Through Proper Channel

Subject : University Examinations - D.M Neurology - August 2006 Session Dissertation Revised and Re-Submitted.

Ref. : 16473 / COE II (1) / 2006, dated 23.10.06
Reg. No : 16031101. Dissertation No. 106.

After Completion of my D.M. neurology course from Madurai Medical College, in Aug'2006, I Appeared for the examination held in Aug'2006. My. Reg. No is 16031101. My dissertation No. 106

In reference to letter No. (1) I am Re. submitting my dissertation after correction.

The following objections were raised and reply are given below

11. Proforma is revised as per the suggestion.
12. Objection raised in title: Title not convincing to type of work.

Correction : Title revised, in relation to type of work carried out.

Introduction : Re-organized in relation to proposed work.

Follow up period :

Comments	:	Not given clearly
Reply	:	Highlighted in the methodology section

Results :

Comments : Errors in results noticed

Reply : Results have been revised in relation to analysis and organized in logical manner.

Review of Literatures:

Comment : Presentation to be modified

Reply : Modified and revised as per scientific writing by (Peat J. etal) By word Viva Publication Pvt. Ltd.

Aim of The Study :

Comment : Specific aspect of the study not fulfilled.

Reply : The aim of the study has been re-organised

Methodology :

Comment : Not spelled out

Reply : Spelled out in a structured manner

Discussion :

Comment : Not organized

Reply : Revised and presented in an appropriate manner

Conclusion :

Comment : Sub. optimal

Reply : Revised based on re-analysis.

I am herewith sending my revised dissertation.

I thank the examiner for high lighting the various lacunae in the study.

I had made an earnest attempt to correct it.

Thanking you

Nagercoil,
- 11- 06

Yours faithfully,

A. Sethu Ram